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Fatigue and the wear-off effect in adult patients with common variable immunodeficiency

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Summary

Patients with common variable immunodeficiency (CVID) have increased fatigue compared with the general population. Fatigue is associated with lower quality of life (QoL), which is associated with higher mortality in CVID. This study aimed to determine the prevalence of self-reported fatigue for patients with CVID and to identify its possible drivers and burden on QoL. We analysed data from the 2013 Immune Deficiency Foundation (IDF) treatment survey. Answers were included from 873 CVID patients who responded (respondents). Of the 873 respondents included in the analysis, 671 (76·9%) reported fatigue, of whom 400 (83·7%) were receiving intravenous (i.v.) immunoglobulins (IVIG) and 271 (68·6%) were receiving subcutaneous (s.c.) immunoglobulins. This difference in fatigue between patients receiving IVIG and SCIG was statistically significant ($P < 0·001$). Dose and frequency of immunoglobulin replacement therapy (IgGRT) did not affect fatigue prevalence. Fatigued patients on IVIG reported greater infection rates and required more anti-microbials during the wear-off period. Fatigued patients reported worse health status than non-fatigued patients, and had lower rates of employment, education, household income and school attendance than their non-fatigued counterparts. Fatigue is increased in CVID, especially among patients receiving IVIG, compared to SCIG. Fatigue has a significant impact on QoL and productivity in patients with CVID. Further studies to identify the mechanisms of fatigue are warranted to help advance therapeutic measures to treat this disease and improve patients' QoL and wellbeing.

Keywords: common variable immunodeficiency, fatigue, Immune Deficiency Foundation, immunoglobulin replacement therapy, wear-off effect

Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic primary immune deficiency (PID) in adults [1]. The prevalence of CVID ranges from 1 : 10 000 to 1 : 100 000 [2,3]. The hallmark of CVID is poor antibody production and recurrent infections. In addition, 20% of CVID patients have non-infectious complications, such as autoimmunity, chronic lung/gastrointestinal disease and malignancy [4,5]. Despite treatment options such as immunoglobulin (Ig)G replacement therapy (IGGRT), the mortality rate in CVID remains high, with a median age of death of 43 years [4].

Recently, using health care-provider-reported data, we have shown that fatigue is significantly increased in CVID patients compared with the general population [6]. We have also shown that patients who report fatigue have a significantly lower quality of life (QoL) than those in a normative sample of the general US population ($P < 0·05$) [7]. Poor QoL is an independent predictor of mortality in CVID [8], especially in patients with severe non-infectious complications [9]. Importantly, it has been projected that improving the QoL score by one point may reduce the risk of death by 2–3% [8]. Focusing on the drivers of QoL in CVID provides an untapped opportunity to improve outcomes, and potentially survival.

The purpose of this study was to determine the prevalence of patient-reported fatigue among CVID patients, define the burden of fatigue on affected patients and evaluate its possible drivers using data from the Immune Deficiency Foundation (IDF) 2013 treatment survey.

Methods

Survey subjects

The initial survey was mailed on 20 December 2013. A second mailing to non-respondents was conducted on 27 January 2014. Data collection was completed on 28 February 2014. As reported previously [7], 4000 surveys were mailed and 1608 were received. For this analysis, responses were included from respondents with CVID (n = 73) who had answered fatigue questions (Q43a) and who were receiving IgGRT. Some questions were left unanswered, and therefore the actual number of responses included per question varied. Only those individuals identified as adult people with CVID were included in the analysis. Proxy responses were excluded from our analysis, ensuring that only self-reported data were used in the analysis.

Survey design and administration

As previously reported [7], this was a two-part mail survey, comprising a 75-question survey (IDF survey; S1) and the SF-12v2 survey (https://www.optum.com/optum-outcomes/what-we-do/health-surveys/sf-12v2-health-survey.html). These surveys are designed for adults aged ≥ 18 years. The questionnaires were self-administered and anonymous.

Fatigue definition

Fatigue status was based on patient response to question Q43a: 'Does the patient experience periods of fatigue or low energy between Ig therapy treatment (wear-off)?'. Patients were defined as non-fatigued if they responded 'never' and defined as fatigued if they responded 'always or occasionally'. The decision to combine always and occasionally responses was based on preliminary analysis that showed similar patterns in patients reporting always and occasionally.

For fatigue as a side effect of IgGRT, data were analysed from question 39: 'During the past 12 months, has he/she experienced any of the following during or after Ig therapy?' and question 51b: 'overall bother due to IgG therapy'.

Immunoglobulin replacement therapy dosing calculation

Monthly dose (mg/kg) was calculated for each patient based on responses to questions Q30, Q31, Q35, Q47b (IDF survey; Supporting information, Fig. S1). Based on their responses, we clustered patients into the following groups: < 400 mg/kg; 400–600 mg/kg, which is considered the standard replacement dose; 600 1000 mg/kg, which is usually an adjusted replacement dose or > 1000 mg/kg, which is an immunomodulatory dose.

Statistical analysis

Descriptive analysis was performed to evaluate the characteristics of the fatigued patients. This analysis was performed to determine the sex, average age, race, level of education, household income, employment status, IgGRT type of the individuals affected with fatigue and wear-off between treatments. Each variable with missing responses was evaluated to determine if the missing data made up a significant percentage of the results. If > 30% of patient responses were missing a particular data element, the variable was omitted from the study.

A χ^2 test was used to determine if IgGRT type [intravenous Ig (IVIG) *versus* subcutaneous Ig (SCIG)], immune modulation *versus* immune replacement dosage and occurrence of respiratory tract infections (RTIs) had any influence on patient-reported fatigue. χ^2 analysis was also used to determine if any correlations existed between perceived health, household income, education level and productivity to reported fatigue.

Fisher's exact test was used to determine if there were any significant differences between reported fatigue and the total monthly IgGRT dose or treatment frequency for both SCIG and IVIG patients. This test was used instead of the χ^2 test here because it is more effective on small sample sizes.

Multivariate analysis. To determine which variables to consider for building the multivariate logistic regression model for fatigue prediction, a univariate analysis was run and variables with a $P < 0{\cdot}25$ were considered for the multivariate logistic regression model. The backwards stepwise selection method was used to build the multivariate model. All variables were entered into a preliminary model and the P-values were reviewed. The highest P-value was eliminated, and the model was re-run. This continued at each step of the model until all P-values were considered significant ($P < 0{\cdot}05$).

Results

Demographics and clinical characteristics

The median age of CVID cohort was 55 years. Most of these CVID patients (95%) identified themselves as white non-Hispanic. Approximately 50% had a college degree or higher, but 39% reported a household income less

Table 1. Demographics and characteristics of CVID patients: all patients

	All patients (873)
Characteristic	***n*** (%)
Sex	
Female	685 (78·5%)
Male	188 (21·5%)
Current age, years	
Median (range), all patients	55 (18–100)
Median (range), females	56 (19–100)
Median (range), males	53 (18–89)
Race	
White, non-Hispanic	829 (95·0%)
Other	30 (3·4%)
Missing/no response	14 (1·6%)
Level of education	
8th grade or less	1 (0·1%)
Some high school	10 (1·2%)
High school graduate/GED	110 (12·6%)
1–3 years of college	232 (26·6%)
4-year college graduate	259 (29·7%)
Graduate degree	250 (28·6%)
Missing/no response	11 (1·3%)
Household income	
$0–24 999	177 (20·3%)
$25 000–49 999	161 (18·4%)
$50 000–74 999	171 (19·6%)
$75 000–99 000	106 (12·1%)
$100 000 or more	198 (22·7%)
Missing/no response	60 (6·9%)
Employment status	
Employed full time	277 (31·7%)
Employed part time	85 (9·7%)
Unemployed, looking for work	16 (1·8%)
Student	18 (2·1%)
Homemaker	55 (6·3%)
Disabled/too ill to work	232 (26·6%)
Other	137 (15·7%)
Retired	0 (0%)
Missing/no response	53 (6·1%)
IGGRT type	
SCIG	395 (45·2%)
IVIG	478 (54·8%)

When comparing the average age of male *versus* female patients, there is a significant difference in age for all patients (P = 0·0032). CVID = common variable immunodeficiency; GED = general educational development.

than $50 000 and 26·6% reported that they were disabled or too ill to work. All 873 patients reported taking IgGRT; 45·2% of CVID patients were receiving SCIG and 54·8% were receiving IVIG (Table 1).

Prevalence of patient-reported fatigue

Of the 873 CVID patients who answered the question about fatigue, 671 (76·9%) reported experiencing fatigue, either always or occasionally, while 202 (23·1%) reported never experiencing fatigue. The median age of fatigued CVID patients was 56 years; females accounted for 80% of fatigued patients and most were white non-Hispanic. More than 50% of fatigued patients had a college degree or higher level of education, 40% reported an annual household income of less than $50 000 and more than one-third reported being disabled/too ill to work. All fatigued patients were receiving immunoglobulin replacement therapy (IGGRT). Age, sex, race and employment status were similar between fatigued and non-fatigued patients. Fatigued patients were significantly less likely to have a 4-year college graduate degree or higher (P = 0·002), a higher percentage of household income less than $100 000 or more ($P$ < 0·001) and were more likely to receive IVIG compared to SCIG (P < 0·001; Table 2). Overall, the patient-reported prevalence of fatigue in our data set was high and aligns with our previously documented overrepresentation of fatigue in patients with CVID, as determined from physician-reported data [6].

Relationship of demographic variables to fatigue

Given the burden of patient-reported fatigue in CVID, we wanted to identify the demographic variables that were associated with increased fatigue. We started by analysing the impact of age on fatigue, keeping in mind that the survey was designed for adult patients. We observed a statistically significant increase in the presence of fatigue with increased age, starting from age 18 to 64 years. For example, 83·1% of patients who were aged 55–64 years reported fatigue. In contrast, only 63.6% of patients who were aged 18–24 years reported fatigue (P = 0.007) and 69·4% of patients who were aged 25–34 years reported fatigue (P = 0·010). We noted a decline in fatigue prevalence after the age of 65 years – 71·2% of patients who were aged 65–74 years reported fatigue, significantly less frequent than that for patients age 55–64 years (P = 0·004), Fig. 1.

Next, we evaluated the impact of sex on fatigue. Previous studies in the general population have described a difference in reported fatigue between males and females [10]. Our results showed that a greater percentage of females reported fatigue than did males (79·1 *versus* 68·6%, P = 0·002). This sex bias may have occurred in part because almost 80% of respondents were female.

Previous reports have described impacts of socioeconomic status on fatigue in certain contexts. Therefore, we wanted to assess the relationship between those socioeconomic variables (education, income and occupation) and fatigue in our data set. We found that patients with less education than a college degree had a higher percentage of reported fatigue compared with patients with a college degree or higher (82·2 *versus* 72·9%, P = 0·002),

Table 2. Demographics and characteristics of common variable immunodeficiency (CVID) patients: fatigued and not fatigued patients

Characteristic	Fatigued patients (671) *n* (%)	Not fatigued patients (202) *n* (%)
Sex		
Female	542 (80·8%)	143 (70·8%)
Male	129 (19·2%)	59 (29·2 %)
Current age, years		
Median (range)	56 (18–100)	54 (19–89)
Median (range), females	56 (20–100)	56 (19–83)
Median (range), males	56 (18–82)	49 (19–89)
Race		
White, non-Hispanic	635 (94·6%)	194 (96·0%)
Other	23 (3·4%)	7 (3·5%)
Missing/no response	13 (1·9%)	1 (0·5%)
Level of education*		
8th grade or less	1 (0·2%)	0 (0%)
Some high school	6 (0·9%)	4 (2·0%)
High school graduate/GED*	94 (14·0%)	16 (7·9%)
1–3 years of college	189 (28·2%)	43 (21·3%)
4-year college graduate*	193 (28·8%)	66 (32·7%)
Graduate degree*	178 (26·5%)	72 (35·6%)
Missing/no response	10 (1·5%)	1 (0·5%)
Household income**		
$0–24 999*	153 (22·8%)	24 (11·9%)
$25 000–49 999	129 (19·2%)	32 (15·8%)
$50 000–74 999*	128 (19·1%)	43 (21·3%)
$75 000–99 999*	82 (12·2%)	24 (11·9%)
$100 000 or more*	133 (19·8%)	65 (32·2%)
Missing/no response	46 (6·9%)	14 (6·9%)
Employment status		
Employed full time	189 (28·2%)	88 (43·6%)
Employed part time	59 (8·8%)	26 (12·9%)
Unemployed, looking for work	14 (2·1%)	2 (1·0%)
Student	12 (1·8%)	6 (3·0%)
Homemaker	43 (6·5%)	12 (5·9%)
Disabled/too ill to work	213 (31·7%)	19 (9·4%)
Other	99 (14·8%)	38 (18·8%)
Retired	0 (0%)	0 (0%)
Missing/no response	42 (6·3%)	11 (5·5%)
IGGRT type****		
SCIG	271 (40·4%)	124 (61·4%)
IVIG	400 (59·6%)	78 (38·6%)

*There is a significant difference in the level of education between fatigued and not fatigued patients at the following levels: high school graduate/general educational development (GED) *versus* 4-year college graduate ($P = 0{\cdot}021$); high school graduate/general educational development (GED) *versus* graduate degree ($P = 0{\cdot}004$); and 4-year college graduate *versus* graduate degree ($P = 0{\cdot}008$). **There is a significant difference in the household income between fatigued and not fatigued patients at the following income levels: $0–24 999 *versus* $50 000–74 999 ($P = 0{\cdot}005$); $0–24 999 *versus* $75 000–99 000 ($P = 0{\cdot}041$); $0–24 999 *versus* $100 000 or more ($P < 0{\cdot}001$); and $50 000–74 999 *versus* $100–000 or more ($P = 0{\cdot}009$). ***There is a significant difference in the employment status between fatigued and not fatigued patients for employed *versus* unemployed ($P < 0{\cdot}001$). ****There is a significant difference in IGGRT type between fatigued and not fatigued patients ($P < 0{\cdot}001$).

Fig. 1. Fatigue was more prevalent in patients who reported being unemployed than in those who were employed (91·5 *versus* 68·5%, $P < 0.001$) and those who reported their employment status as 'other' (73·3%, $P < 0{\cdot}001$) Fig. 1. Additionally, we noted an inverse correlation between household income and fatigue prevalence. There was a significant difference in reported fatigue between the $0–24 999 income bracket (86·4% fatigued) and the $50 000–74 999 bracket (74·9% fatigued, $P = 0{\cdot}006$), the $75 000–99 999 bracket (77·4% fatigued, $P = 0{\cdot}049$) and the $100 000 or more bracket (67·2% fatigued, $P < 0{\cdot}001$). There was also a significant difference in patients reporting fatigue between the $25 000–49 999 (80·1% fatigued) and the $100 000 or more bracket (67·2% fatigued, $P = 0{\cdot}006$) Fig. 1. Thus, in our survey population, age, sex and socioeconomic variables were all significantly associated with fatigue prevalence in patients with CVID.

Relationship between medical variables and fatigue

While demographic characteristics were expected to relate to fatigue to some degree, we were most interested in relationships between medical variables and fatigue in patients with CVID. We started by examining the presence of medical impairment before CVID diagnosis. In total, 464 of the 873 (53·2%) respondents with available answers reported the presence of permanent impairment before their CVID diagnosis. Permanent lung damage was the most frequent impairment, occurring in 287 (32·9%) patients, followed by reported permanent gastrointestinal (GI) impairment in 150 (17·2%) patients. With patient-reported data it is difficult to surmise exactly what these permanent impairments and chronic conditions may be, so it is not surprising that fatigue was significantly higher in patients reporting permanent impairment than in those who reported no permanent impairment 385 (83·0%) *versus* 286 (69·9%), $P < 0{\cdot}001$. Fatigue was more prevalent in those reporting permanent lung impairment (236, 82·2%) than in those who did not (435, 74·2%, $P = 0.008$). Similarly, fatigue was more prevalent in those who reported GI impairment (135, 90·0%) than in those who did not (536, 74·1%, $P < 0{\cdot}001$).

Infections are a hallmark of immune abnormality, and their incidence has been correlated inversely with QoL [7]. Thus, we evaluated the association between fatigue and infection frequency. We focused our analysis on respiratory tract infections (RTIs) reported within the last 12 months, including bronchitis, ear infection, sinusitis and pneumonia, as they were the most common infections reported by patients in the data set. Two hundred and seventy-two patients reported no RTIs within the last 12 months, 204 patients reported one

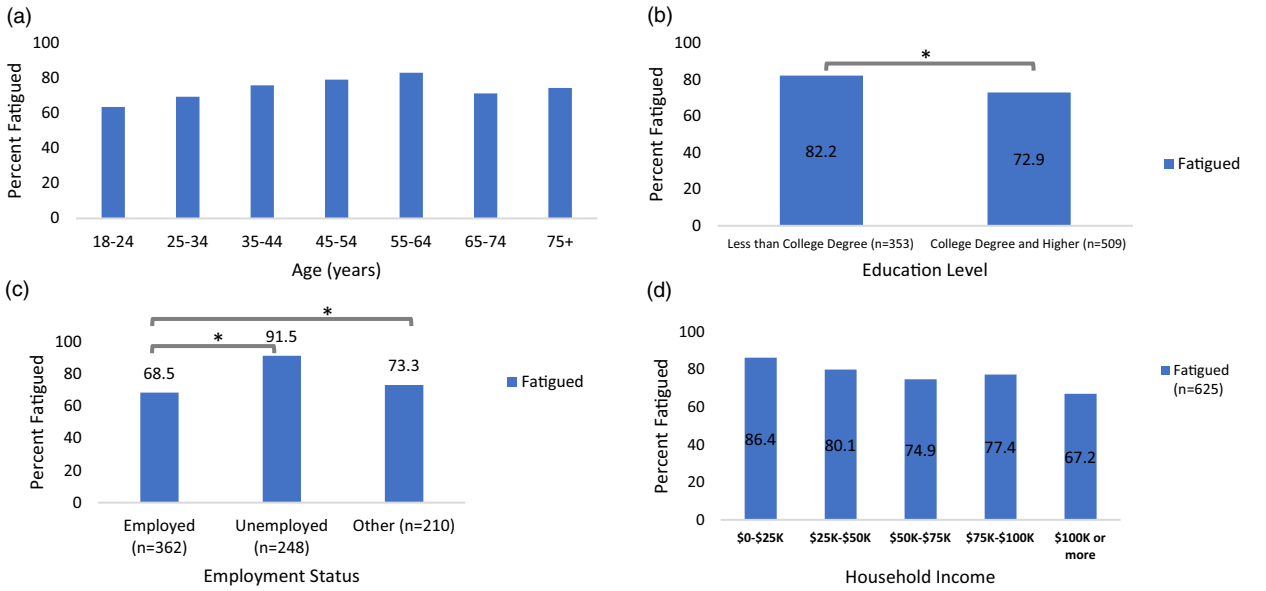

Fig. 1. Relationship between fatigue and key patient demographics. (a) Relationship between fatigue and age: the prevalence of fatigue increased in a statistically significant manner with increasing age, starting from age 18 to age 64 years, and then decreased after age 65 years. (b) Relationship between fatigue and education level: fatigue is more prevalent in patients with an education level less than a college degree than it is in patients with a college degree or higher, $*P = 0{\cdot}002$. (c) Relationship between fatigue and employment status: fatigue was more prevalent in unemployed patients than in employed patients. 'Employed' was defined as full- and part-time employment. 'Unemployed' was defined as unemployed and disabled/too ill to work. 'Other' was defined as students, homemakers and other, $*P < 0{\cdot}001$. (d) Relationship between fatigue and household income: the lower the household income, the higher the fatigue prevalence.

to two infections, 190 patients reported three to four infections and 251 patients reported more than five upper respiratory infections (URIs) within the last 12 months. Fatigue prevalence increased as the frequency of infections increased: no RTIs *versus* three to four RTIs ($P = 0{\cdot}002$); no RTIs *versus* five or more RTIs ($P < 0{\cdot}001$); one to two RTIs *versus* three to four RTIs ($P = 0{\cdot}001$) and one to two RTIs *versus* five or more RTIs ($P < 0{\cdot}001$) per year (Fig. 2). We performed a separate analysis to determine if history of pneumonia was associated with higher fatigue compared to other respiratory tract infections, and we found no statistically significant difference in fatigue prevalence among patients reporting pneumonia *versus* sinusitis, otitis media and bronchitis without reporting pneumonia within the last 12 months (data not shown). Thus, both the prevalence of organ system impairment and incidence of RTI were positively associated with fatigue. Interestingly, this association between fatigue and RTI seems to be true only in patients who experience fatigue as a wear-off effect. When the data were re-analysed by including patients who reported no fatigue at wear-off ($n = 65$) (most of those patients reported fatigue as a side effect of IGRT), we found no significant difference in the number of reported RTI between fatigued and non-fatigued ($P = 0{\cdot}996$).

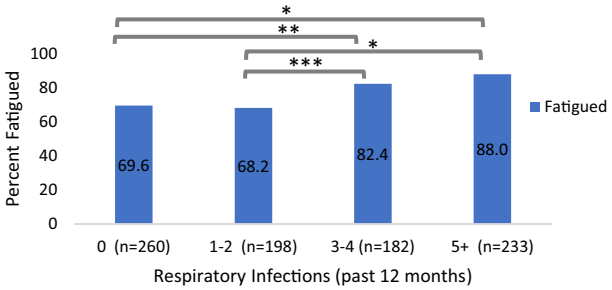

Fig. 2. Numbers of upper respiratory tract infections during the past 12 months as stratified by presence of fatigue. Fatigue was more prevalent in patients reporting more frequent infections within the last 12 months. $*P < 0{\cdot}001$, $**P = 0{\cdot}002$, $***P = 0{\cdot}001$.

Relation of immunoglobulin replacement therapy to fatigue

We were interested in the relationship between IgGRT and fatigue. First, we examined the impact of the route of IgGRT on fatigue. Of 873 CVID patients who responded to the fatigue questionnaire, there were 395 patients receiving SCIG and 478 receiving IVIG (45·2 *versus* 54·8%, respectively). Patients receiving IVIG had a significantly higher rate of fatigue than those receiving SCIG [400 (83·7%) *versus* 271 (68·6%), $P < 0{\cdot}001$ (Fig. 3)]. Notably, more males reported receiving IVIG therapy (62·8 *versus*

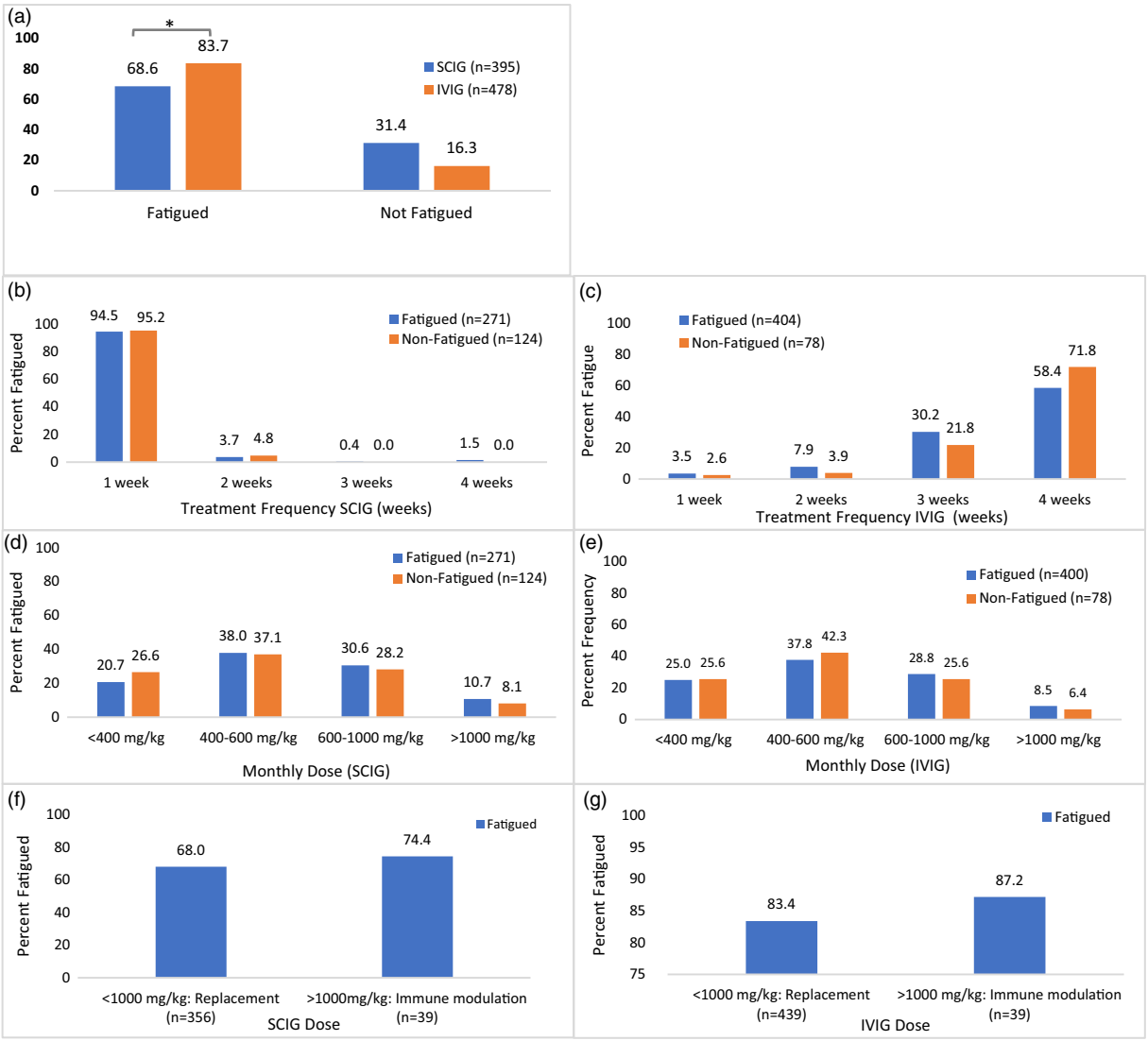

Fig. 3. Relationships between fatigue in patients with common variable immunodeficiency (CVID) and mode of immunoglobulin G replacement therapy (IgGRT) received. (a) Fatigue prevalence is higher in intravenous immunoglobulin (IVIG) than in subcutaneous immunoglobulin (SCIG), *$P < 0{\cdot}001$. (b) Fatigue prevalence by treatment frequency in SCIG; no significant differences in fatigue were found between weekly and bi-weekly doses. (c) Fatigue prevalence by treatment frequency in IVIG; no significant differences in fatigue were found between weekly doses and doses received every 2, 3 or 4 weeks or more. (d) Fatigue by monthly dose in SCIG; no significant differences in fatigue were found between reported concentrations of monthly doses. (e) Fatigue by monthly dose in IVIG; no significant differences in fatigue were found between reported monthly doses. (f) Fatigue in SCIG as replacement *versus* immunomodulatory dose; no significant differences in fatigue were found as a function of replacement *versus* immunomodulatory dose. (g) Fatigue in IVIG as replacement dose *versus* immunomodulatory dose; no significant differences in fatigue were found in reported fatigue for IVIG a replacement dose *versus* an immunomodulatory dose.

52·6%), while more females reported receiving SCIG (47·5 female *versus* 37·2% male, $P = 0{\cdot}013$).

Given the increased prevalence of fatigue in CVID patients receiving IVIG, we conducted multiple analyses to identify the variable(s) that could have contributed to the increase prevalence of fatigue in this subset of the cohort. We compared the total monthly dose and dosing frequency for both SCIG and IVIG treatment regimens, but could not identify a specific dose or dosing frequency pattern associated with increased fatigue. The fatigue rate was not statistically significantly different between patients receiving an immunomodulatory dose (> 1000 mg/kg) compared to replacement dose (< 1000 mg/kg) in both patients receiving IVIG and SCIG, $P = 0{\cdot}372$.

Fatigue and the treatment 'wear-off' effect

Finally, we wanted to evaluate specifically what is referred to as 'wear-off' fatigue. There have been a number of associations proposed for wear-off. We wanted to determine if fatigue could be a phenomenon associated with

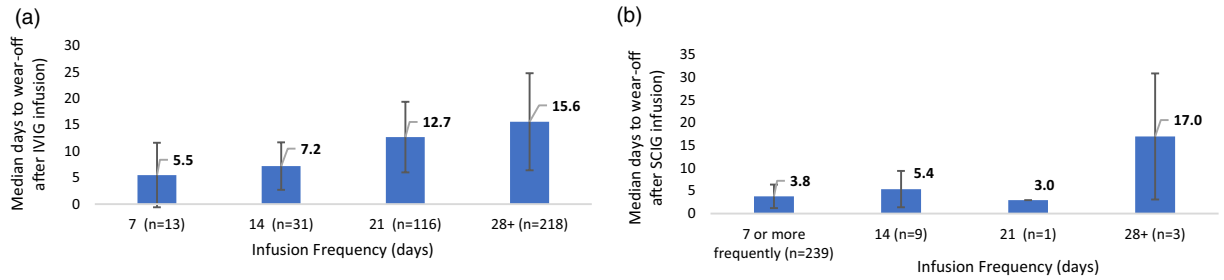

Fig. 4. Relationships between wear-off effect and the infusion frequency. (a) Intravenous immunoglobulin (IVIG) wear-off effect, reported as a function of infusion frequency; the number of days after infusion at which patients reported experiencing the wear-off effect correlated with the frequency of the infusion. (b) Subcutaneous immunoglobulin (SCIG) wear-off effect, reported as a function of infusion frequency; the number of days after infusion at which patients reported experiencing the wear-off effect correlated with the frequency of the infusion.

wear-off by evaluating question 43b more closely, in which details regarding the timing between the infusion and the feeling of the 'wear-off' effect were provided. This allowed us to evaluate the frequency of infusion and its relationship with fatigue from the wear-off effect, as reported by patients, in the days before their next infusion. In patients receiving IVIG, there was a correlation between the frequency of infusions and the mean numbers of days after infusion in which patients felt the wear-off effect/fatigue. For example, in patients receiving IVIG every 21 days, they felt wear-off/fatigue on day 12 of the infusion cycle (Fig. 4). A similar pattern, although less clear, is observed in SCIG, in which patients receiving SCIG every 7 days reported feeling wear-off/fatigue on day 4 post-infusion. Correlations with alternative dosing frequencies were not observed; however, these other dosing frequencies were reported less often, resulting in a small sample size. This limitation might have prevented our ability to detect such a pattern in another dosing frequency (Fig. 4). However, while these analyses delineate a more common incidence of fatigue at a particular point in the midst of infusion cycles, they do not associate this variety of patient-reported fatigue as a traditional wear-off concept, i.e. one that is most pronounced just prior to the next infusion.

Q43c2 specifically asks: 'Does the wear-off result in: need for antibiotics?' by comparing the need for antibiotics due to wear-off effects between patients on IVIG *versus* SCIG. We noted a significant difference in the reported need for antibiotics due to the wear-off effect between fatigued patients receiving IVIG *versus* SCIG (33·3 *versus* 21·8%, $P = 0{\cdot}001$), although the total number of infections was not different in the IVIG compared to the SCIG groups.

Finally, we explored the possibility that was fatigue was a side effect of IgGRT. Specifically, question 39 of the survey asked about symptoms experienced as side effects of IgGRT. One of the questions was: 'During the past 12 months due to Ig therapy [did you experience]: fatigue?'. Five hundred and seventeen (59·2%) of respondents reported experiencing fatigue as a side effect of IgGRT therapy. Of those, 6·1% reported feeling fatigue during the infusion, 32·5% after the infusion and 20·6% reported experiencing fatigue both during and after infusion. Fatigue was reported more frequently as a side effect in patients receiving IVIG than in those receiving SCIG [311 (65·1%) *versus* 206 (52·2%), $P < 0{\cdot}001$]. Patients who experienced fatigue also reported other side effects of IgGRTl, such as headache and fever. Treatment dose and frequency of infusion were not associated with a significant difference in fatigue, which was reported as a side effect for patients receiving either treatment (data not shown).

We then cross-compared the total fatigue population to those reporting it as a side effect. In this analysis, 67·4% of patients who reported fatigue due to wear-off also reported fatigue as a side effect, while 32·2% of patients who did not have fatigue due to wear-off reported fatigue as a side effect ($P < 0{\cdot}001$). More than half the fatigued patients (51·8%) experienced fatigue due to wear-off and fatigue as a side effect, and 25·1% of patients experienced fatigue due only to wear-off (not as a side effect), 7·4% of patients experienced fatigue as a side effect only (not due to wear-off) and 15·7% of patients experienced no fatigue (wear-off or side effect).

Impact of fatigue on perceived health and missed work/school days

We were interested in identifying any relationships between fatigue and patient-reported health status. We observed an inverse correlation between perceived health status and incidence of fatigue: as the perceived health status decreased, the percentage of fatigued patients increased (Fig. 5, $P < 0{\cdot}001$). Finally, we evaluated the impact of fatigue on patient productivity. Seven hundred and twenty-one patients provided answers to both fatigue and missed work/school days questions. Of these, 329 (78·3%) of fatigued patients reported missing school and work days compared with only 91 (21·7%) non-fatigued patients

Table 3. Variables predictive of fatigue in patients with common variable immunodeficiency (CVID)

Variable		Odds ratio (95% CI)	*P*-value
IGRT Route	IVIG *	2·22 (1·50–3·29)	0·00
RTI	Having 3–4 RTIs increases the odds of fatigue**	2·14 (1·22–3·75)	0·008
	Having 5 or more RTIs increases the odds of fatigue**	2·48 (1·39–4·45)	0·000
Perceived Health	Perceived health as 'excellent/very good'***	0·51 (0·33–0·79)	0·003
	Perceived health as 'poor/very poor'***	2·32 (1·40–3·83)	0·001
Headache	Headache****	2·42 (1·64–3·58)	0·00
Household income	Annual household income greater than $100 000*****	0·53 (0·28–0·98)	0·042

IGRT = immunoglobulin replacement therapy; IVIG = intravenous immunoglobulins; RTI = respiratory tract infection; SCIG = subcutaneous immunoglobulins; CI = confidence interval.

*Compared to SCIG; **compared to 0 RTI; ***compared to 'good' perceived health; ****as side effect of IGRT; *****compared to those with household income less than $25 000.

(P = 0·012, Fig. 5). Thus, similar to results from analyses of other diseases, patient-reported fatigue in patients with CVID correlates inversely with QoL and perceived health status.

In the above analysis, a univariate analysis was run for each of the variables to determine if, independently, they were predictors of fatigue. Backwards stepwise regression was then performed using variables that were determined to be predictors of fatigue at the univariate level to determine the best-fitting multivariate model which would be used to examine relationships between multiple variables that, together, significantly predict fatigue.

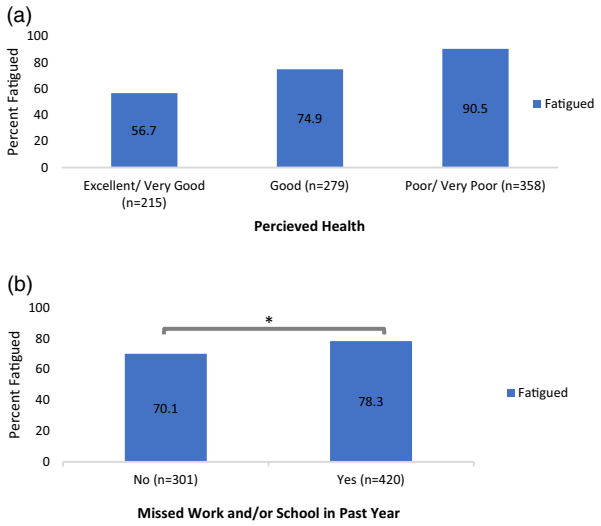

Fig. 5. Impact of fatigue on quality of life (QoL), perceived health status and missed work/school days. (a) Patient-reported health status as a function of fatigue; fatigue was more frequently reported in patients with poor perceived health status than in those with good and very good/excellent perceived health status. (b) Effect of fatigue on missed work/school days; fatigued patients reported statically significantly higher number of missed work/school days than non-fatigued patients, *P = 0·012.

The final multivariate model included IgRT treatment, perceived health, RTI (categorical), household income and headache. When holding all other variables in the model constant (IgRT = SCIG; perceived health = good; RTI = no infections; headache = none), the variables that predicted outcomes in the multivariate analysis (Table 3) were the route of IGRT, where patients receiving IVIG had an increase in the odds of fatigue [odds ratio (OR) = 2·22; P = 0·000] compared to those on SCIG, perceived health, as patients whose perceived health was reported as 'excellent/very good' had a decrease in the odds of fatigue (OR = 0·51; P = 0·003) compared to those who reported their health as 'good'. Patients whose perceived health was reported as 'poor/very poor' had an increase in the odds of fatigue (OR = 2·32; P = 0·001) compared to those who reported their health as 'good' the number of RTIs, as patients who reported three to four RTIs had an increase in the odds of fatigue (OR = 2·14, P = 0·008) compared to those with no RTIs, and patients who reported five or more RTIs had an increase in the odds of fatigue (OR = 2·48, P = 0·002) compared to those with no RTIs. Having headache as a side effect of IGRT increased the odds of fatigue by (OR = 2·42, P = 0·000). Finally, an annual household income greater than $100 000 had a decrease in the odds of fatigue (OR = 0·53), P = 0·042 compared to those with annual household income less than $25 000.

Discussion

Fatigue is a known and important variable in human health. It is associated with worse QoL in several important maladies which, in turn, is associated with survival.

We have previously described an increased incidence of fatigue in USIDnet clinical reported data for CVID patients [6]. Here, we sought to build upon this work and extend it by moving directly into patient-reported data. Patient-reported data are generally held to be more accurate, as health care-reported data frequently under-estimate key signals [11], or in other cases do not correlate with patient-reported data [11–13]. Thus, we felt that such an analysis was essential to extend our initial findings regarding an increased signal for fatigue in from physician-reported data [14].

Our analysis of fatigue in patients with CVID revealed several interesting findings. First, it confirmed our previous observation that patients with CVID have a significantly higher prevalence of fatigue than does the general population [6]; those findings were not surprising, given the difference in the data source – the data from the IDF survey were patient-reported, while the USIDnet data were reported by health care providers.

In our univariate analysis, we identified several independent predictors of fatigue among patient with CVID, including female sex and having lung and GI impairment. However, when fitted into a multivariate model their influence on fatigue became insignificant when paired with the other variables in the predicted model. The increased prevalence in females over males could be skewed, at least in part, by the nature of our data set; most respondents to this survey were female. However, previous studies showed that, in the general population, fatigue is reported more frequently by females than in males [10,15]. We have shown previously that primary antibody deficiency patients with non-infectious complications have a higher rate of fatigue [6]. Similarly, CVID patients with chronic GI and lung disease had lower QoL and higher mortality rate than did those free of such complications [8,16], and while permanent lung damage was not a significant variable in predicting fatigue in multivariate analysis, having permanent lung damage increased the odds of fatigue in a univariate analysis [OR = 1·46, P = 0·045, 95% confidence interval (CI) = 1·01–2·13].

The relationship between age of patients with CVID and fatigue was interesting, as we found that the fatigue prevalence increased as age increased from 18 to 64 years, and then decreased at age 65. We have noted a similar pattern in our previous analysis from the USIDnet [6]. One possible explanation to the shift in this trend at age 65 could be retirement, as 65 is the average retirement age for the US population. Studies using longitudinal modelling suggested that retirement was associated with a significant reduction in both mental and physical fatigue, especially in individuals with chronic conditions [17]. Although the majority of fatigued patients were white, most survey respondents reported their race as white, which could have led to under-representation of the other races. Previous studies have shown that non-white individuals (e.g. Native American, African American and Hispanic) have higher rates of fatigue than do white individuals [18–20]

It was interesting to find that patients on IVIG reported having more RTIs and required more antibiotic treatment, due perhaps to the wear-off effect of their infusions, than did patients receiving SCIG. However, the frequency of infections reported overall was similar between patients receiving either treatment. This finding is compatible with previous studies that showed that IVIG and SCIG are equally effective in protecting against infections [21–25]. However, patients on IVIG reported higher infection rates towards the end of the infusion cycle, which was associated with the wear-off effect of IgGRT [26,27], and patients who switched from IVIG to SCIG reported less wear-off effect and less fatigue [28–30]. While these data would not provide any rationale for a priority consideration of therapeutic modality, they might equate to the consideration of offering SCIG treatment to patients receiving IVIG can also experience fatigue.

Along these lines, we noted a striking difference in fatigue prevalence between patients receiving IVIG and those receiving SCIG. Patients receiving IVIG reported a significantly higher fatigue prevalence compared to those on SCIG (Fig. 1). To identify the factors that could explain this difference, we conducted several analyses. To our surprise, we found no association between IgGRT dose or frequency of treatment and occurring fatigue. However, we noted that there was a higher than expected percentage of patients who were receiving a dose less than 400 mg/kg, while the standard dose is 400 600 mg/kg [31,32].

The difference in fatigue as a function of the IgGRT administration route could be due to the difference in pharmacokinetics between IVIG and SCIG. In IVIG, IgG enters the vascular compartment in a high concentration, redistributes rapidly into tissue compartments and is then catabolized more slowly [33]; those systemic side effects are thought to cause the acute rise in IgG following the infusion [34] while, in SCIG, IgG initially forms a local depot then reaches the bloodstream indirectly through the lymphatic system, leading to more consistent serum IgG levels and fewer systemic side effects [25]. Indeed, we observed that patients who reported fatigue as a side effect of IgGRT (both IVIG and SCIG) suffered from other side effects of IgGRT, such as headache and fever. Here, we must again point out that we did not have access to medical records to understand the rationale of choosing IVIG *versus* SCIG for those patients or

identifying the IgG trough for those patients. These factors limit the generalizability of these findings. We maintain that the choice of route IgGRT is based on multiple factors, such as accessibility, availability, compliance, cost and others, and is a decision that should be made jointly between the provider and patient. That said, it would again appear reasonable given the now consistent signal across both health care-reported and patient-reported data to inquire about fatigue and consider offering SCIG as an option to patients receiving IVIG who experience fatigue.

However, there is possibly a broader importance to these findings, in that having fatigue is associated with lower QoL [7], which is an independent predictor of survival in CVID patients [8]. Through our analyses, we have identified that fatigue is also associated with poor perception of health status, which is yet another important link to QoL and satisfaction [35,36]. In addition, fatigue in CVID could impose significant financial burden, as fatigued patients were more likely to be unemployed, miss more days of work or school, have lower educational levels and lower annual household income compared to non-fatigued people. Those findings echo similar studies in cancer-related fatigue that showed fatigued cancer patients to have lower annual income [37,38], more likely to miss work days, change their employment status and resolve to disability or unpaid medical or family leave [39]. Thus, inquiring about the existence of fatigue and using rationale tools to intervene with fatigue would seem to be a relevant practice. What is needed at this point are prospective studies of fatigue in CVID using validated fatigue instruments as well as potential studies of interventions that have been proven to be of benefit to fatigue in other diseases.

Limitations

Our study has important limitations that we need to emphasize. First, fatigue was not measured using validated tools. Rather, it was determined based on responses to a single question in the survey. This clearly impeded our ability to define fatigue further into its components (e.g. physical, mental) or measure fatigue severity. Secondly, the single fatigue question was combined with a question concerning the wear-off effect. There were no data available on the IgG trough to correlate with the fatigue responses, which prevented us from differentiating between general fatigue and fatigue caused by the wear-off effect. Depression is sometimes associated with fatigue; however, the survey did not include information about depression, and hence we could not assess if fatigue is associated with depression. Additionally, this survey is based on patient-reported data; patients were asked to report their health status within the last 12 months and requested patients to provide information on their IgGRT dosing and frequency. These answers were not validated using medical records, which could lead to recall bias. Another limitation to this study is selection bias; this survey was distributed to patients registered in the IDF database in the United States and only approximately 50% of patients responded, which might limit the generalizability of the study. These limitations call clearly for a prospective study of fatigue in patients with CVID using validated fatigue instruments. Despite these limitations, however, we believe that this study sheds light on fatigue, a topic that is seldom discussed or treated in CVID patients, and uncovers an important dimension of fatigue's impact on QoL, wellbeing and productivity. We have identified several factors associated with fatigue that warrant further evaluation via prospective studies to develop effective strategies and targeted plans for managing fatigue in patients with CVID, hopefully further improving their outcomes and QoL.

Conclusions

Fatigue is increased in patients with CVID, especially in patients who are receiving IVIG. Fatigued patients reported having more infections, particularly towards the end of their infusion cycle. Fatigue led to a significant impact on patient-reported QoL and patient-reported health status and was associated with lower rates of employment, education and household income, as well as an increase in missed days from work or school. Given the substantial effect of fatigue in QoL, health care providers should strive to examine fatigue as a possible issue in their patients with CVID and might consider the use of SCIG in patients receiving IVIG who experience substantive levels of fatigue. Further studies to identify the mechanisms of fatigue are warranted to help advance therapeutic measures to treat it, thereby improving patients' QoL and wellbeing.

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Author contributions

J. H. conceived and designed the study, provided analysis and interpretation of data, co-designed study figures and tables, drafted the paper and approved the final version. C. K. performed data analysis, co-designed figures and tables, assisted in data interpretation and approved the final version. N. L. R. assisted in interpretation of data, revised the paper critically for important intellectual content and approved the final version. F. O. S. assisted in interpretation of data, revised the article critically for important intellectual content, and approved the final version. C. S. designed the 2013 treatment survey, assisted in interpretation of data, revised the paper critically for important intellectual content and approved the final version. J. S. O. assisted in interpretation of data, revised the paper critically for important intellectual content and approved the final version.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site:
Fig. S1. Fatigue in common variable immunodeficiency